Azathioprine plus prednisone in treatment of pemphigoid

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Summary and conclusions

Twenty-five patients taking part in a controlled trial to compare azathioprine plus prednisone with prednisone alone in the treatment of pemphigoid were followed up for three years. Results showed that the addition of azathioprine 2·5 mg/kg body weight daily reduced the total maintenance dose of prednisone needed by about 45%, with no increase in serious side effects or mortality. The suggestion that azathioprine might increase the risk of disseminated malignancy in elderly patients was not supported.

We conclude that in future trials the combination of azathioprine with prednisone should be used as the standard treatment for comparison.

Introduction

Azathioprine and prednisone are powerful drugs with potentially serious side effects. In some of these, such as the risk of infection, the drugs may be synergistic, and animal studies have shown that immunosuppressives combined with steroids in high dosage produce a higher mortality than either drug used alone.[1] Azathioprine is now often combined with prednisone to treat pemphigoid, an autoimmune blistering disease of the elderly. This combination has never been subjected to a controlled trial, but results of an uncontrolled study suggested that immunosuppressive treatment might increase the risk of disseminated malignancy in elderly patients with pemphigoid.[2] We report on a controlled trial of azathioprine with prednisone versus prednisone alone in the treatment of pemphigoid.

Methods

In 1973 the dermatologists at this hospital agreed to allocate to the trial all new patients with pemphigoid. Patients were included only if the diagnosis was supported by clinical, histological (a subepidermal blister), and immunological evidence (IgG directed against the basement membrane zone on direct immunofluorescence). Patients who satisfied these diagnostic criteria were excluded from the trial only if they were unlikely to attend for regular follow-up or if there was some definite reason (such as known malignancy or hypertension) for not receiving azathioprine or prednisone. Advanced age or other illness was not a contraindication to inclusion because we wished the results of the trial to be relevant to standard clinical practice. Every new patient was admitted to hospital and received oral prednisone as necessary (30-80 mg daily) for one week to suppress new blisters. Baseline tests (blood counts, liver function tests, estimations of urea and fasting blood sugar concentrations, chest radiography, and skin biopsy) were performed during this week, and the consultant decided whether to include the patient in the trial. Once included, each patient was randomly assigned to either the control group (prednisone alone) or the azathioprine group (prednisone with azathioprine) by the ward sister, who drew a marked paper from an envelope. The control group continued to receive prednisone as dictated by their clinical state. The azathioprine group also continued with prednisone but in addition received oral azathioprine, 2·5 mg/kg body weight daily. This group had a blood test (haemoglobin concentration, white cell count, and platelet count) on alternate days for 10 days, then weekly for one month, every two weeks for six months, and every four weeks thereafter. When the white cell count fell below 3×10^9/l (3000/mm^3) the azathioprine dose was halved; if it had fallen below $1{\cdot}5 \times 10^9$/l we would have stopped treatment, but this complication did not occur. The control group did not receive such frequent blood tests but were seen at four- to six-weekly intervals, and regular attempts were made in both groups to reduce prednisone treatment by 5-mg decrements to zero when the disease was suppressed. Once patients had stopped prednisone and remained free of rash for three months the azathioprine was then also gradually reduced to zero. When relapse occurred in patients in the azathioprine group both drugs were restarted together and prednisone withdrawal was reinstituted when the rash was suppressed.

Results

Twenty-five patients completed a three-year follow-up (table I). The mean dose of prednisone received over the three years by the patients who were also receiving azathioprine was 3688 mg compared with 6732 mg received by the control patients; this 45% reduction in steroid dosage in the azathioprine group was significant ($P < 0{\cdot}01$).

The three deaths that occurred in the azathioprine group were thought to be unrelated to treatment, but in the control group two of the four deaths (due to bronchopneumonia and a massive haemorrhage from peptic ulcer) were probably related to the prednisone treatment (table II).

Side effects in the azathioprine group were minimal. Only two patients developed mild leucopenia, which was reversed when the azathioprine dosage was reduced. In the control group one patient developed severe hypertension and had to be changed to treatment with azathioprine, after which he became normotensive and the rash was successfully controlled.

Discussion

Several uncontrolled studies have shown that azathioprine suppresses pemphigoid, but the effect of this treatment on the long-term prognosis has not been adequately studied.[3 4] Burton

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TABLE I—*Clinical details, mean annual prednisone dosage, and outcome in 25 patients with pemphigoid who completed three-year follow-up*

Treatment	Clinical details			Mean annual dose of prednisone (mg)			Outcome after three years			
	No of patients	Sex	Mean age at onset (years)	Year 1	Year 2	Year 3	No of deaths	No in remission with no treatment	No well but needing treatment	No withdrawn owing to side effects
Azathioprine + prednisone	12	6 M, 6 F	75·6	2980	400	308	3	7	2	0
Prednisone alone (controls)	13	3 M, 10 F	74·1	4362	1650	720	4	3	5	1

TABLE II—*Details of patients who died in azathioprine group (azathioprine plus prednisone) and control group (prednisone alone)*

Age at death (years)	Treatment at death	Cause of death	Time from onset
	Azathioprine group		
65	Nil	Cerebrovascular accident	3 years
85	Azathioprine + prednisone	Cerebrovascular accident	1 month
85	Azathioprine + prednisone	Congestive cardiac failure	10 months
	Control group		
76	Prednisone 20 mg/day	Bronchopneumonia	1 year
76	Prednisone 15 mg/day	Massive haemorrhage from peptic ulcer	7 months
77	Prednisone 20 mg/day	Mesenteric thrombosis	2 months
80	Nil	Cerebrovascular accident	6 months

and Greaves[2] reported that two out of 12 patients in a prospective but uncontrolled trial died of cancer within two years after starting azathioprine treatment. They suggested that the risk of disseminated malignancy after suppression of immunosurveillance may be greater in patients with pemphigoid than in others because of the suspicion that the disease may occasionally be secondary to occult or overt malignancy.[5 6] Even if there is no causal relation between cancer and pemphigoid, few would dispute that occult malignancy is more likely to be present in elderly patients than in those from younger age groups, and patients with pemphigoid, being elderly, might be particularly at risk from immunosuppressive drugs. Our controlled study, in which patients were carefully followed for three years, showed no evidence of this, and azathioprine produced a significant decrease in steroid requirements with minimal side effects.

A recent uncontrolled study, in which 14 patients with mild pemphigoid were treated with prednisone alone and 15 more severe cases received azathioprine 1·5 mg/kg plus prednisone, showed that even a low dose of azathioprine exerts a steroid-sparing effect with minimal toxicity.[7]

We conclude that azathioprine plus prednisone is superior to prednisone alone in the treatment of pemphigoid, and future trials should use this combination as the standard for comparison.

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Relation of high-density lipoprotein cholesterol concentration to type of diabetes and its control

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Summary and conclusions

Serum cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were measured in 192 diabetics (94 with juvenile-onset and 98 with maturity-onset diabetes) and 177 non-diabetic controls. Hb A_{1C}, an index of blood sugar control, was also measured in the diabetics. Serum cholesterol concentrations were similar in all the diabetics and controls, but HDL cholesterol concentrations were lower in patients with maturity-onset diabetes than in those with juvenile-onset diabetes and controls. There was no correlation in diabetics between HDL cholesterol and Hb A_{1C}.

We conclude that HDL cholesterol concentrations are abnormally low in patients with maturity-onset diabetes but essentially normal in those with juvenile-onset diabetes. They are not related to diabetic control.

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Introduction

Serum cholesterol may be partitioned into high- and low-density lipoprotein fractions (HDL and LDL cholesterol respectively). Results of previous lipid studies have generally emphasised that serum cholesterol and low-density lipoproteins have a positive relation with coronary heart disease. Recently an inverse relation has been found between serum HDL cholesterol and coronary heart disease,[1] and a low concentration of serum HDL cholesterol has been suggested as the major lipid risk factor.[2 3] In diabetes mellitus low serum HDL cholesterol concentrations have been associated with the increased incidence of coronary heart disease in women.[4] It has been claimed that poorly controlled diabetics have significantly lower serum HDL cholesterol concentrations than those with good blood sugar control,[5] and that patients receiving sulphonylurea treatment have lower concentrations than those treated with insulin or with dietary measures alone.[6]

We have analysed concentrations of serum cholesterol and its HDL fraction in relation to the type of diabetes—that is, juvenile-onset or maturity-onset. We have also studied the glycosylated Hb A_{1C} concentration, which has been regarded as an integrated index of blood sugar control over the previous weeks.[7 8]

Subjects and methods

We studied 192 diabetic patients attending the hospital diabetes clinic. Ninety-four (45 male and 49 female) patients had juvenile-onset diabetes (age less than 40 years at time of diagnosis and needing